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(WO/2000/010526) NEW ORAL FORMULATION FOR 5-HT4 AGONISTS OR ANTAGONISTS

Biblio. Data	Description	Claims	National Phase	Notices	Documents
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Latest bibliographic data on file with the International Bureau

Publication Number: WO/2000/010526 International Application No.: PCT/EP1999/006083

Publication Date: 02.03.2000

International Filing Date: 19.08.1999

Chapter 2 Demand Filed: 28.02.2000

Int. Class.: A61K 31/00 (2006.01), A61K 31/404 (2006.01), A61K 9/20 (2006.01)

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Priority Data: 9818340.3 21.08.1998 GB
9823477.6 27.10.1998 GB
9910320.2 05.05.1999 GB
9911059.5 12.05.1999 GB

Title: NEW ORAL FORMULATION FOR 5-HT4 AGONISTS OR ANTAGONISTS

Abstract: The present invention relates to a pharmaceutical composition, in particular to a composition for administering active agents which are poorly soluble in aqueous media, and/or which are acid sensitive.

Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW.
African Regional Intellectual Property Org. (ARIPO) (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW)
Eurasian Patent Organization (EAPO) (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM)
European Patent Office (EPO) (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE)
African Intellectual Property Organization (OAPI) (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Publication Language:

English (EN)

Filing Language:

English (EN)

**(WO/2000/010526) NEW ORAL FORMULATION FOR 5-HT4 AGONISTS OR ANTAGONISTS**

Biblio. Data

Description

Claims

National Phase

Notices

Documents

Note: OCR Text

NEW ORAL FORMULATION FOR 5-HT4 AGONISTS OR ANTAGONISTS The present invention relates to a pharmaceutical composition, in particular to a composition for administering active agents which are poorly soluble in aqueous media and/or which are acid sensitive. More particularly, the present invention relates to a pharmaceutical composition for administering active agents acting on the gastro-intestinal system. The present invention also relates to a process for manufacturing such compositions. The term "pharmaceutical" also covers veterinary use.

Pharmaceutical compositions containing active agents which are poorly soluble in aqueous media and/or acid sensitive are difficult to manufacture. One of the problems that may occur concerns adsorption of the active agent on the process equipment during the manufacturing process. Due to the poor solubility of such active agents it is also difficult to obtain pharmaceutical compositions which upon administration have a good dissolution rate. As a further problem, active agents may be degraded, e. g., chemically, during a manufacturing process using acidic conditions or during the storage of the composition.

The present invention provides compositions and processes which avoids or minimise one or more of the above problems.

We have now surprisingly found that it is possible to produce a pharmaceutical composition for administering of active agents which are poorly soluble in aqueous media, e. g., pure water, and/or acid sensitive, and which upon administration has good dissolution properties, a good bioavailability and is surprisingly efficacious.

The present invention provides in one aspect a solid oral pharmaceutical composition, e. g., a tablet, comprising an active agent which is poorly soluble in aqueous media, and/or acid sensitive, and a disintegrant, e. g., a super-disintegrant, which is present in an amount of at least 15% by weight based on the total weight of the composition.

By "poorly soluble" is meant an active agent having a solubility in aqueous media more than 0.001% and less than 10%, e. g., less than 1%, e. g., less than 0.1%, e. g., less than 0.05%, e. g., less than 0.02%, at room temperature, e. g., 25°C. By "acid sensitive" is meant an active agent which under even slightly acidic conditions, e. g., at pH 6, may be transformed to a significant extent in a degradation product, e. g., by chemical degradation, which may have no or changed activity, e. g., within 2 hours. Examples of compounds are known in the art and may be ascertained by routine experimentation.

By "disintegrant" is meant a substance or mixture of substance added to a solid pharmaceutical composition, e. g., a tablet, to facilitate its break-up or disintegration after administration in order that the active ingredient is released from the composition as efficiently as possible to allow for its rapid dissolution (see e. g. "Remington's Pharmaceutical Science" 18th edition (1990), "The Theory and Practice of Industrial Pharmacy" Lachman et al. Lea & Febiger (1970)).

We have also found difficulties on producing stable commercially acceptable formulations, e. g., tablets, of compounds such as those disclosed in EP505322 (herein incorporated by reference) and which are useful as 5-HT4 receptor agonists or partial agonists.

A preferred 5-HT4 partial agonist disclosed in EP505322 is Tegaserod (3- (5-methoxy-1H-indol-3-yl-methylene) -N-pentylcarbazimidamide) (example 13) of formula which is referred hereinafter as Compound A, or a pharmaceutically acceptable salt form thereof, e. g., the hydrogen maleate (hereinafter "hml") salt. Compound A has a solubility of about 0.02% at 25°C in water and is acid sensitive. We have found that compositions may be produced which give good

absorption even in the stomach. We have also found that Compound A may be adsorbed by certain excipients so that its dissolution upon administration may be substantially reduced. Little has been published in detail on 5-HT4 receptor agonists, partial agonists or antagonists biopharmaceutical properties, e. g., their site of action is not known.

The present invention provides in a further aspect pharmaceutical compositions allowing a complete dissolution of 5-HT4 receptor agonists, partial agonists or antagonists, e. g., Compound A, when administered to humans, e. g., patients, in need thereof. These compositions allow a good bioavailability and are surprisingly efficacious. Moreover, they are stable and well reproducible. A process for their preparation is also provided.

Active agents which may be used in compositions according to the present invention are more generally those acting on the gastro-intestinal system, e. g., serotonergic active agents, e. g., full agonists, partial agonists and antagonists of 5-HT4 receptors to the extent they are poorly soluble and/or acid sensitive. They are preferably in salt form, e. g., hydrogen maleate or hydrochloride, and may be in free form.

The 5-HT4 receptor is a cloned species of the serotonin receptor family which comprises at least 14 distinct G protein-coupled receptors (the receptor ionophore of the 5-HT3 subtype excluded). Four splice variants of the human receptor, 5-HT4A, 5-HT4B, 5-HT4c, and 5-HT4D, have been identified which differ in the length and sequence of the protein's C terminus (Blondel et al., FEBS Letters (1997) 412 : 465-474 ; Blondel et al., J. Neurochem. (1998) 70 : 2252-2261). Biochemical characterisation of 5-HT4 receptors revealed a positive coupling to adenylyl cyclase. 5-HT4 receptor expression in man has been found in the brain, the gut, the atria, the urinary bladder and kidneys.

Compounds capable of acting on the serotonin receptor are substituted benzamides, e. g., cisapride, renzapride, zacopride, clebopride, cinitapride, mosapride, lintopride, metoclopramide, or benzoic esters, e. g., RS 23597-190, SB 204070, SB 207710, or aminoguanidines, zacopride, prucalopride, SB205149, SC53116, RS67333, RS67506, BIMU 1, BIMU 8, (S) -RS 56532, Tropisetron, Atosetron, GR 113808, GR 125487, SB 207266, RS 23597, RS 39604, RS 100235, DAU6285, SC 53606, 3- (5-hydroxy-7- methyl-1 H-indol-3-yl- methylene)-N-pentyl-N-methyl-carbazimidamide, indazole-3-carboxamides, 2-oxobenzamidazole-3-carboxamides (as disclosed in EP 908 459 which is herein incorporated by reference) etc.

5-HT4 receptor agonists are considered as compounds which can activate 5-HT4 receptors under quiescent/resting conditions (complete or partial activation). As 5-HT4 receptor full agonists or partial agonists one may cite (S) -zacopride, cisapride, prucalopride, SB 205149, SC 53116, RS 67333, RS 67506, BIMU 1, BIMU 8, (S) -RS 56532 and Compound A, particularly its hydrogen maleate salt.

5-HT4 receptor antagonists are considered as compounds which do not activate 5-HT4 receptors but act as inhibitors of agonists at 5-HT4 receptors. As 5-HT4 receptor antagonists one may cite GR 113808, GR 125487, SB 203186, SB 204070, SB 207266, RS 23597, RS 39604, RS 100235, DAU 6285, SC 53606, 3- (5-hydroxy-7-methyl-1 H-indol-3-yl-methylene) -N-pentyl-N-methyl-carbazimidamide.

5-HT4 receptor agonists are useful for the prevention and treatment of gastro-intestinal motility disorders, e. g., Irritable Bowel Syndrome (IBS), Gastro-Esophageal Reflux Disease (GERD), Functional Dyspepsia (FD) and Post Operative Ileus (POI).

In a preferred embodiment, the composition of the invention comprises 20 to 60%, e. g., 30 to 50%, e. g. 40% by weight of disintegrant based on the total weight of the composition. We have observed that the use of such a high percentage of disintegrant further improves the dissolution rate in aqueous media, but also prevents the active agent from adsorbing on excipients.

As disintegrants the composition of the invention may comprise : crospovidone (molecular weight >106), e. g., Polyplasdone XL®, Kollidon CLX Polyplasdone XL-10®, - pregelatinised starch (MW : 30 000 - 120 000), e. g., starch 1500, STA-Rx 1500, - sodium starch glycolate (MW : 500 000 - 1 000 000), e. g. Primojele, - carboxymethylcellulose calcium (CMC-Ca), - carboxymethylcellulose sodium (CMC-Na) (MW : 90 000 - 700 000), e. g., Ac-Di-So, - sodium alginate, or a mixture thereof.

Preferably, the disintegrant is crospovidone which is preferably water insoluble. Preferably it rapidly exhibits high capillary or pronounced hydration capacity with little tendency to gel formation. Preferably the particle size is from about 1 to 500 micrometers. Preferred particle size distribution is less than 400 micrometers, e. g., for Polyplasdone XL®, less than 80 micrometers, e. g., less than 74 micrometers for, e. g., Polyplasdone XL-100, approximately 50% greater than 50 micrometers and maximum of 1 % greater than 250 micrometers in size for, e.g., Kollidon CL®. A preferred crospovidone is Polyplasdone XL(IN), e.g., with a density of about 0.213 g/cm³ (bulk) or 0.273 g/cm³ (tapped).

The pharmaceutical composition of the invention may further comprise one or more excipients.

The composition may further comprise one or more lubricants, e. g., in an amount within the range of from, e. g., 1 to 20%, e. g., from 5 to 15%, e. g., 10% by weight of the composition.

Examples of such lubricants include - glyceryl mono fatty acid, e. g., having a molecular weight of from 200 to 800, e. g., glyceryl monostearate (e.g., Myvaplex®, USP quality) - polyethylene glycol (PEG), having a molecular weight of from 100 to 10000, e. g., 1000 to 8000, e. g., 2000 to 6000, e. g., 2500 to 5000, e. g., Macrogol 4000 (Pulver) BP, - hydrogenated castor oil (e.g., Cutina®), and the like or a mixture thereof.

In a preferred composition the lubricant is glyceryl monostearate. The lubricant properties of such preferred composition may be improved by adding polyethylene glycol (PEG), e. g., Macrogol 4000 (Pulver) BP.

The composition of the invention may comprise one or more surfactants, e. g., in an amount in the range of from 0.1 to 10%, e. g., 1 to 5%, e. g., 2% by weight of the total composition.

Pharmaceutically suitable surfactants may be non-ionic or anionic.

As non-ionic surfactants one may use : - polyoxyethylene-sorbitan-fatty acid esters (polysorbates ; MW : 500 to 2000), e. g., mono- and tri- lauryl, palmityl, stearyl and oleyl esters, e. g., TweenO, e. g., Tween 80® ; Other conventional excipients which may optionally be present in the composition of the invention include preservatives, stabilisers, anti-adherents or silica flow conditioners or glidants, e. g., silicon dioxide (e.g., Syloid®, Aerosil®) as well as FD&C colours such as ferric oxides.

Other excipients disclosed in the literature, as for instance in Fiedler's "Lexicon der Hilfsstoffe", 4th Edition, ECV Aulendorf 1996 and "Handbook of Pharmaceutical Excipients" Wade and Weller Ed. (1994), the contents of which are incorporated herein by reference, may be used in the pharmaceutical compositions according to the invention.

The invention is particularly useful for pharmaceutical compositions containing an active agent, e. g., an 5HT4 receptor agonist, partial agonist or antagonist, e. g., compound A, e. g., the hydrogen maleate salt, which is present in an amount within the range of from about 0.2% to about 20%, e. g., 0.5 to 15%, and preferably from about 1% to about 10% by weight of the composition.

A preferred composition of the invention may comprise from about 0.5 to about 15% by weight of active agent, e. g., a 5HT4 receptor agonist, e. g., compound A, e. g., the hydrogen maleate salt, from 20 to 60% by weight of disintegrant, e. g., crospovidone, from 1 to about 20% by weight of a lubricant, e.g., monoglycerylstearate, from 0.1 to about 10% by weight of a surfactant, e. g., poloxalkol, from about 10 to 50% by weight of a diluent, e. g., lactose, and from 1 to 10% by weight of a binder, e.g., hydroxypropylmethyl cellulose (e.g. HPMC- 3). From 1 to 10% by weight of PEG may also be added.

The weight ratio of the active agent to the disintegrant may be from 1 : 1 to 1 : 400, e. g., 1 : 5 to 1 : 100, 1 : 8 to 1 : 50, e. g., 1 : 16 to 1 : 20.

In a further aspect the present invention provides a pharmaceutical oral, e. g., tablet, composition comprising one of the active agents cited above, e. g., a 5-HT4 agonist, partial agonist or antagonist, e. g., Tegaserod, said composition having dissolution characteristics in water or in USP buffers pH 6.8 and 7.5 of : time (minutes) amount (percentage) 5 30 - 90 -

polyoxyethylene fatty acid esters (MW : 500 to 5000), e.g., Myrjeor Cetiol®; - polyoxyethylene-polyoxypropylene co-polymers, e.g., having a molecular weight of from 1000 to 20 000, e.g., 6 000 to 15 000, e.g., 7 000 to 10 000, e.g., Pluronic or Emkalyx®; - polyoxyethylene-polyoxypropylene block co-polymers e.g., having a molecular weight of from 1000 to 20 000, e.g., 6 000 to 15 000, e.g., 7 000 to 10 000, e.g., Poloxamer 188®; - reaction products of a natural or hydrogenated castor oil and ethylene oxide, e.g., Cremophor®; - dioctylsuccinate or di-2-ethylhexyl- succinate; - propyleneglycol mono- and di-fatty acid (e.g. Ce-Cs) esters, e.g., Miglyol®; or mixtures thereof.

As suitable anionic surfactants one may use, e.g., sodium laurylsulfate or docusate sodium.

Unless where otherwise stated fatty acid or carbon containing chain is from about 8 to 22 carbon atoms, e.g., C₈.

The composition of the invention may comprise one or more binders, e.g., in an amount in the range of from 1 to 10%, e.g., 2 to 8%, e.g., 5% by weight. One may particularly use : - hydroxypropylmethylcellulose, e.g., having a molecular weight of from 10 000 to 1 500 000, e.g., HPMC-3 (3mPa-s) (e.g. Pharmacoat®, Methocel®), - polyvinylpyrrolidone, e.g., having a molecular weight of from 2500 to 3 000 000, e.g., 8 000 to 1 000 000, e.g., 10 000 to 400 000, e.g., 30 000 to 50 000 (e.g., Kollidon®, Plasdone®), - potato starch, wheat starch, corn starch, e.g., having a molecular weight of from 30 000 to 120000, or a mixture thereof.

The composition of the invention may comprise one or more diluents such as lactose, mannitol, sucrose, calcium sulphate, calcium phosphate, microcrystalline cellulose (Avicel®) in an amount within the range of from, e.g., 10 to 70%, e.g., 20 to 50%, e.g., 30% by weight of the composition. Preferably, the diluent is lactose, e.g., lactose 200 mesh (e.g., from DMV® or Alpvit®), e.g., the monohydrated form.

15 80 - 100 30 95 - 100 60 100 For example a composition according to the invention, e.g., comprising Tegaserod as the active agent, may have dissolution characteristics in water or in USP buffers pH 6.8 and 7.5 of : time (minutes) amount (percentage) 5 48.9 15 95.5 30 99.7 60 100 In a further aspect the present invention provides a pharmaceutical oral, e.g., tablet, composition comprising one of the active agents cited above, e.g., a 5-HT₄ agonist, partial agonist or antagonist, e.g., Tegaserod, wherein in use 80% of said active agent is released in water or in USP buffers pH 6.8 and 7.5 within 5 minutes.

In a further aspect, the present invention provides the use of at least 15% by weight of a disintegrant in the manufacturing of pharmaceutical composition for the administration of an acid sensitive and/or poorly soluble, e.g., in aqueous media, active agent, e.g., a 5-HT₄ receptor agonist, e.g., compound A, e.g. the hydrogen maleate salt.

The pharmaceutical compositions of the present invention are useful in the known indications of the particular active agent incorporated therein.

The exact amounts of active agent and of the formulation to be administered depend on a number of factors, e.g. the condition to be treated, the desired duration of treatment and the rate of release of active agent.

For example, the amount of the active agent required and the release rate thereof may be determined on the basis of conventional in vitro or in vivo techniques, determining how long a particular active agent concentration in the blood plasma remains at an acceptable level for a therapeutic effect. Examples of doses provided in a solid formulation, e.g., a tablet, are, for Irritable Bowel Syndrome (IBS), 1 mg to 12 mg of active agent, for functional dyspepsia (FD) and gastroesophageal reflux disease (GERD), 0.2 to 2mg of active agent, in particular compound A, e.g. the hydrogen maleate salt, per day for a 70 kilogram mammal, e.g. humans, and in standard animal models. The increased tolerability of the active agent, in particular compound A, e.g. the hydrogen maleate salt, provided by the compositions may be observed in standard animal tests and in clinical trials.

The pharmaceutical composition of the invention comprising a 5-HT₄ receptor agonist, partial agonist or antagonist is particularly useful for improving sensory perception of rectal distension, e.g. for the treatment of anal incontinence, or for preventing, modulating or treating visceral pain or discomfort.

5-HT4 receptor agonists, partial agonists or antagonists, e. g. as disclosed in EP-A1- 505, 322, on the basis of observed activity, e. g. stimulatory effect on the peristaltic reflex in the isolated guinea-pig ileum, e. g. as described in EP-A1- 505,322, have been found to be useful for the treatment of gastro-intestinal motility disorders, for example to normalise or to improve the gastric emptying and intestinal transit in subjects having a disturbed motility, e. g. in irritable bowel syndrome.

In accordance with the present invention, it has now surprisingly been found that 5-HT4 receptor agonists, partial agonists or antagonists have a beneficial effect, e. g. they exert modulating effects, on the sensory perception of rectal distension and on visceral sensitivity or perception.

It is admitted that receptor properties are not uniform throughout the gut and that the type of afferent innervation reflects the quality of sensations originating from a particular organ. For example, the rectum belongs to those parts of the gastro-intestinal tract from which also non-painful sensations arise, in contrast to the colon from which only painful sensations emanate.

Anal incontinence may be due to functional disturbances of the main anal continence mechanisms. Anal continence appears to be based on a co-ordinated functioning of the neuromuscular machinery managing rectal sensation and compliance, the recto-anal inhibitory reflex, reflex contractions of the external anal sphincter and the puborectalis muscle. Although skeletal muscle (external sphincter and puborectalis) contractions are of great importance in the maintenance of continence, it is probably the triggering effect of rectal sensation and perception that plays a crucial role and, in fact, is frequently abnormal in incontinent patients. Anal incontinence is a dysfunction which occurs particularly in diabetics and the elderly population.

There is a medical need for modulating visceral sensitivity, discomfort or pain in patients suffering from gastro-intestinal disorders and for a treatment of anal continence dysfunctions.

In accordance with the particular findings of the present invention, there is provided : 1. 1. A method for preventing, modulating or treating viscera !, e. g. abdominal, pain or discomfort in a subject in need thereof, which method comprises administering to said subject an effective amount of a 5-HT4 receptor agonist, partial agonist or antagonist or a pharmaceutically acceptable salt thereof.

1. 2. A method for modulating visceral sensitivity or perception in a subject in need thereof, which method comprises administering to said subject an effective amount of a 5-HT4 receptor agonist, partial agonist or antagonist or a pharmaceutically acceptable salt thereof.

1. 3. A method for stimulating 5-HT4 receptors present on afferent nerve terminals, particularly on extrinsic neurones of the gut, in a subject in need thereof, which method comprises administering to said subject an effective amount of a 5-HT4 receptor agonist or partial agonist or a pharmaceutically acceptable salt thereof.

1. 4. A method for modulating visceral sensitivity, discomfort or pain via stimulation of 5- HT4 receptors present on afferent nerve terminals, particularly on extrinsic neurones of the gut, in a subject in need thereof, which method comprises administering to said subject an effective amount of a 5-HT4 receptor agonist or partial agonist or a pharmaceutically acceptable salt thereof.

1. 5. A method for regulating or stabilising myenteric plexus-afferent fibers in a subject in need thereof, which method comprises administering to said subject an effective amount of a 5-HT4 receptor agonist or partial agonist or a pharmaceutically acceptable salt thereof.

1. 6. A method for improving sensory perception of rectal distension in a subject in need thereof, which method comprises administering to said subject an effective amount of a 5-HT4 receptor agonist, partial agonist or antagonist or a pharmaceutically acceptable salt thereof.

1. 7. A method for treating anal continence dysfunctions in a subject in need thereof, which method comprises

administering to said subject an effective amount of 5-HT4 receptor agonist, partial agonist or antagonist or a pharmaceutically acceptable salt thereof.

As alternative to the above the present invention also provides : 2. A 5-HT4 receptor agonist, partial agonist or antagonist or a pharmaceutically acceptable salt thereof for use in a method as defined under 1. 1 to 1. 7 above ; or 3. A 5-HT4 receptor agonist, partial agonist or antagonist or a pharmaceutically acceptable salt thereof for use in the manufacture of a pharmaceutical composition for use in a method as defined under 1. 1 to 1. 7 above ; or 4. A pharmaceutical composition for use in a method as defined under 1. 1 to 1. 7 above comprising a 5-HT4 receptor agonist, partial agonist or antagonist or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable diluents or carriers therefor, e. g. a composition such as disclosed hereinabove.

Preferred compounds for use in accordance with the invention include e. g. those listed hereinabove, particularly 5-HT4 receptor full agonists or partial agonists, e. g. (S) -zacopride, cisapride, prucalopride, SB 205149, SC 53116, RS 67333, RS 67506, BIMU 1, BIMU 8, (S) -RS 56532, especially Compound A and particularly its hydrogen maleate salt, more preferably selective 5-HT4 receptor agonists or partial agonists, and 5-HT4 receptor antagonists, e. g. Tropicsetron, GR 113808, GR 125487, SB 204070, SB 207266, RS 23597, RS 39604, RS 100235, DAU 6285, SC 53606, 3- (5-hydroxy-7-methyl-1 H-indol-3-yl- methylene) -N-pentyl-N-methyl-carbazimidamide etc. By selective is meant a compound which does not substantially bind to or stimulate the serotonin 5-HT3 receptor. A group of compounds excludes Tropicsetron.

Utility of a 5-HT4 receptor agonist, partial agonist or antagonist in the prevention, modulation or treatment of visceral, e. g., abdominal pain or discomfort or modulation of visceral sensitivity or perception or regulation or stabilisation of myenteric plexus-afferent fibers, is demonstrated in convenient tests, e. g., in accordance with the method hereinafter described.

Decerebrate, anaesthesia-free cats under continuous monitoring of blood pressure are paralysed by alcuronium chloride dissolved in rheomacrodex i. v. (200 Rg/kg initially and supplementary doses of 100 Rg/kg, if necessary), and artificially ventilated. Single unit activity of afferent fibres are recorded in a monopolar fashion from peripheral endings of centrally cut filaments of sacral dorsal roots. Tension receptors are identified by probing of their receptive fields in the wall of the mobilise rectum. Thereafter, the response of the units to barostat -controlled rectal ramp-distension is determined. The quantitative response characteristics of the units is evaluated with respect to distension pressure and resulting rectal diameter. Alternatively, the response of the units to pressure-induced peristalsis is measured.

After obtaining 2 distension profiles (5 min each) and/or 10 min of peristalsis under control conditions, a 5-HT4 receptor agonist, partial agonist or antagonist, e. g., Compound A, or vehicle is applied i. v. and the protocol is repeated. Subsequently, the activity of additional units is recorded in the presence of a 5-HT4 receptor agonist, partial agonist or antagonist, e. g., Compound A, or vehicle according to the distension/peristalsis protocol. In this assay, the firing rate of the rectal afferents is reduced after administration of a 5-HT4 receptor agonist or partial agonist at a dose range of from 0. 1 to 3 mg/kg i. v., at distension pressures above 20 mmHg. With Compound A, administered i. v. in incremental doses from 0. 15 to 1. 2 mg/kg, the most prominent inhibition occurs at 50 mmHg and a half-maximal reduction is obtained at about 0. 7 mg/kg.

Utility of a 5-HT4 receptor agonist, partial agonist or antagonist, e. g., Compound A, in the treatment of anal incontinence as well as utility in treating conditions as hereinabove specified, may be demonstrated in accordance with the method hereinafter described.

Intraluminal pressures and reflexes in the last 60 cm of the colon of 10 fasted healthy volunteers are measured by means of perfusion manometry. Three latex balloons positioned at 50,30 and 10 cm, allow volume stimulation. Basal values of colonic intraluminal pressures and reflexes are established. Subsequently, reflex inhibitory relaxations of the internal anal sphincter is triggered by inflating the balloons by 10 ml increments up to a maximum volume of 150 ml. During the inflation phase, two parameters are evaluated : a) the reflux threshold (volume able to induce a substantial pressure decrease of the internal anal sphincter) ; and b) the sensation threshold (volume able to induce a conscious defecation reflex). After the basal recordings, each subject is given a 5- HT4 receptor agonist, partial agonist or antagonist, e. g., Compound A, p. o. and 30 to 90 min later the colonic intraluminal pressure and reflexes are assessed again by the same method. In this test, the 5-HT4 receptor agonist, partial agonist or antagonist, e. g., Compound A, significantly reduced the sensation threshold when administered at a dose of 2-12 mg p. o.

5-HT4 receptor agonists, partial agonists or antagonists, e. g., Compound A, may be administered by any conventional route, in particular enterally, preferably orally, e. g., in the form of tablets or capsules, or parenterally, e. g., in the form of injectable solutions or suspensions or in a suppository form.

5-HT4 receptor agonists, partial agonists or antagonists, e. g., Compound A, may be administered in free form or in pharmaceutically salt form. Such salts exhibit the same order of activity as the 5-HT4 receptor agonists, partial agonists or antagonists in free form.

Daily dosages required in practising the method of the present invention will vary depending upon, for example, the particular compound employed, the mode of administration and the severity of the condition to be treated. An indicated daily dose is in the range of from about 0.05 to about 30 mg, e. g., from about 0.05 to about 5 mg for parenteral use, and of from about 0.1 to about 30 mg for oral use, conveniently administered once or in divided dosages 2 to 4x/day, or in sustained release form. Unit dosage forms for oral administration accordingly comprise from about 0.5 to about 30 mg of 5-HT4 receptor agonist, partial agonist or antagonist, e. g., Compound A, or a pharmaceutically acceptable salt thereof, admixed with an appropriate solid or liquid, pharmaceutically acceptable diluent or carrier therefor.

Furthermore, it has also been found that a 5-HT4 receptor agonist or partial agonist-e.g., Compound A, have a beneficial effect in the prevention or treatment of gastro-intestinal motility disorders, e. g. a stimulatory effect on gastrointestinal motility, in horses and cattle.

Accordingly, there is also provided : 5. 1. A method for preventing or treating gastro-intestinal motility disorders, e. g. by stimulating the motility of the gastro-intestinal tract in horses or cattle in need thereof, which method comprises administering to the horses or cattle an effective amount of a 5-HT4 receptor agonist or partial agonist, e. g., Compound A, or a pharmaceutically acceptable salt thereof.

5. 2. A method for preventing or treating gastro-intestinal motility disorders, e. g. after colic surgery, e. g. post-operative ileus, in horses or cattle in need thereof, which method comprises administering to the horses or cattle an effective amount of a 5-HT4 receptor agonist or partial agonist, e. g., Compound A, or a pharmaceutically acceptable salt thereof.

6. A 5-HT4 receptor agonist or partial agonist, e. g., Compound A, or a pharmaceutically acceptable salt thereof, for use as a veterinary pharmaceutical e. g. for horses or cattle, e. g. in any of the method 5. 1 or 5. 2 indicated above or for use in the manufacture of a veterinary pharmaceutical e. g. for use in a method as defined under 5. 1 or 5. 2.

7. A pharmaceutical composition for veterinary use, e. g. in horses or cattle, e. g. in any of the method 5. 1. or 5. 2. as indicated above, comprising a 5-HT4 receptor agonist or partial agonist, e. g., Compound A, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier therefor, e. g. a composition as disclosed hereinabove.

Preferred 5-HT4 receptor agonists or partial agonists for use in horses or cattle in accordance with the invention include e. g. those listed hereinabove, e. g. (S) -zacopride, prucalopride, SB 205149, SC 53116, RS 67333, RS 67506, BIMU 1, BIMU 8, (S) -RS 56532, especially Compound A and particularly its hydrogen maleate salt, more preferably a selective 5-HT4 receptor agonist or partial agonist.

Utility of a 5-HT4 receptor agonist or partial agonist, e. g., Compound A, in the treatment of post-operative ileus as well as utility in treating conditions as hereinabove specified in horses or cattle, may be demonstrated in accordance with the method hereinafter described.

20 horses having colic syndrome are submitted to abdominal surgery. During surgery supportive therapy is applied to them. At the end of surgery, a specific 5-HT4 receptor agonist or partial agonist, e. g., Compound A, is administered i. v. or i. m., e. g. at a dose of from 0.01 to 10 mg/kg. This dose is repeated every 8 to 24 h until spontaneous defecation is observed. Gastro-intestinal motility is evaluated based e. g. on the presence or absence of gastric reflux as determined by nasogastric intubation, occurrence of borborygmi and timing of defecation after the first injection of the test compound. In this test, the compounds tested, e. g. Compound A, are effective in restoring normal motility function of the equine intestine.

Daily dosages required in practising the veterinary method of the present invention will vary depending upon, for example, the particular compound employed, the mode of administration and the severity of the condition to be treated. An indicated daily dose is in the range of from about 0.01 to about 10 mg/kg, e. g., from about 0.05 to about 5 mg/kg for parenteral use, conveniently administered once or in divided dosages 2 to 4x/day, or in sustained release form.

In a further aspect the invention provides a method for preventing or treating gastro-intestinal motility disorders in a subject, e. g., a human or an animal, in need of such a therapy comprising administering to this subject an effective amount of a composition according to the present invention.

In a further aspect the invention a process is provided for improving dissolution properties in aqueous media of a pharmaceutical composition containing an acid sensitive and/or poorly soluble in aqueous media active agent, e. g., a 5-HT4 receptor agonist, more particularly compound A, e. g. the hydrogen maleate salt.

The pharmaceutical composition of the invention may be prepared by any conventional method known in the art, e. g., by mixing an appropriate amount of the active agent, e. g., a 5-HT4 receptor agonist, with at least 15%, e. g., from 20 to 60%, e. g., from 30 to 50%, e. g., 40%, by weight of a disintegrant based on the total weight of the composition.

It is preferred to formulate in solid form, e. g., unit dosage form. Typical form include capsules and preferably compressed forms such as tablets.

The pharmaceutical composition according to the invention may be prepared by e. g., a wet, e. g., water based, granulation manufacturing process (the process equipment, as glass material, may be pre-treated with a siliconizing agent) comprising the successive steps of : i) pre-mixing the acid sensitive and/or poorly soluble in water active agent, e. g., a 5-HT4 receptor agonist, e. g., compound A, e. g. the hydrogen maleate salt with 60 to 98% of the diluent, and then sieving the resulting mixture, ii) mixing purified water with the binder in a weight ratio of from 1 : 20 to 3 : 20, and stirring until dissolution, iii) adding the surfactant to the solution of ii) and stirring until dissolution, iv) adding the disintegrant, the remaining diluent and 50 to 70% of the first lubricant to the pre mixture of i) and mixing v) wetting the mixture of step iv) with the granulating solution from step iii) while mixing vi) granulating the mixture of step v) by mixing, vii) drying the granulate to reach a required loss on drying, e. g., for the tableting mixture viii) sizing the granulate by sieving.

For tablet manufacturing the granulate from viii) is mixed, e. g., in a free fall mixer, with the rest of the first lubricant and the second one to obtain the desired final tableting mixture which may be compressed into tablets. This may be performed with conventional tableting machines on, e. g., a rotary machine, at compression pressures of, e. g., 2 to 30 KN, e. g. 5 to 27 KN, e. g., 10 to 20 KN (KN = Kilo Newtons).

The composition according to the invention may also be prepared by an alternative wet granulation manufacturing process wherein the pre-mixing and sieving of step i) are not performed. In this case, the active agent, the disintegrant, the diluent and about 60% of the first lubricant are pre-blended together and then wetted with the wetting solution of step iv).

Compositions comprising any of the above-mentioned active agents may be prepared by a process as disclosed above.

If desired the pharmaceutical compositions of the invention are stored under low relative humidity conditions, e. g., rH (relative humidity) less than 50%, e. g., below e. g. 30-50%, and at room temperature, preferably less than 20°C. The compositions provide storage stable systems. Insignificant degradation is detected after storage of up to 1 year at room temperature, e. g., 25 °C.

The compositions of the invention may be packed in conventional manner to keep out humidity, e. g., in a blister pack, optionally with a desiccant.

The compositions of the invention may have a water content of from 0 to 3% based on the total weight of the composition.

The present invention relates in a further aspect to a composition, in particular comprising compound A, as obtained by one of the above processes to provide a small, stable form.

Examples The following examples illustrate the manufacturing, on an industrial scale, of compositions comprising compound A hml using a wet granulation process as disclosed above.

Example 1 A 2 mg tablet formulation may be prepared as described hereinafter. a) Preparation of the granulated materia) Premixing step 1. 4. 432 kg of compound A hml and 28. 688 kg of lactose monohydrate are mixed with an intensive mixer (Colette Grals 300 1 or Fieider) ; mixer speed setting : 1 ; chopper speed setting : 1) for approximately 1. 5 minutes, or with a free fall mixer (Turbu a, Soneco or Rohnrad) 2. The pre-mixture from step 1 is then sieved (oscillating granulator, e.g., Frewitts or Erweka ; mesh size : 0. 8 millimetres).

3. The pre-mixture is divided into two portions of 16. 560 kg.

Preparation of the granulating solution 4. Approximately 40 kg of purified water are weighed out.

5. 3. 600 kg of methylhydroxypropylcellulose 3 maps are added to the purified water from step 4 and this is stirred until dissolution.

6. 1. 440 kg of poloxamer 188 are added to the solution from step 5 while stirring until dissolution.

Granulating step 7. 28. 800 kg of crospovidone, 10. 080 kg of lactose monohydrate and 4. 320 kg of glyceryl monostearate are weighed out.

8. One portion of the premixture from step 3 is added to the excipients from step 7 and this is mixed with the intensive mixer, e.g., Colette Grals 3001 or Fieldere (mixer speed setting : 1 ; chopper speed setting : 1) for approximately 2 minutes.

9. The mixture from step 8 is wetted with the granulating solution from step 6 while mixing with the intensive mixer, e.g., Colette Grals 300 1 or Fietder (mixer speed setting : 1 ; chopper speed setting : 0 ; pumping rate approximately : 4 kg/minute) for approximately 12 minutes.

10. Approximately 2 kg of purified water are weighed out.

11. The vessel from step 6 is rinsed with the purified water from step 10 and this is added to the mixture from step 9 while mixing.

12. The mass is granulated by mixing with the intensive mixer, Colette Grals 300 1 or Fieldero (mixer speed setting : 1 ; chopper speed setting : 1) for approximately 2. 5 minutes.

Drying step 13. The granulate from step 12 is dried in a fluidised air bed drier (e.g., Glatte or Aeromatic) for approximately 65 minutes (inlet air temperature approximately 70°C) to reach the required loss on drying (LOD) for the tableting mixture, i. e., until LOD <4, 4%.

14. The granulate sized by sieving (0. 8 millimetres) with an oscillating sieve granulator, e. g., Frewitt or Erweka.

15. Steps 4 to 14 are repeated with the other portion of step 3. b) Preparation of the tabtettina mixture 16. 8. 640 kg of polyethylene glycol 4000 and 5. 760 kg of glyceryl monostearate are sieved (oscillating granulator, e.g., Frewitte or Erweka@; mesh size : 0. 8 millimetres) 17. The ingredients from step 16 are added to the total mass of granulated material and this is mixed with a free fall mixer, e.g., Soneco or Rohnrad, for approximately 20 minutes (10 rpm) to obtain the desired final tableting mixture. c) Compression step 18. The tableting mixture from step 17 is pressed into tablets using compression pressures of 11,14 or 17 KN on a rotary tableting machine, e.g., Fette@, Korsh@, Keliano or Coart (temperature < 20°C ; rH (relative humidity) < 40%) Example 2 : Composition of a 2 mo tablet (1 mg of base corresponds to 1. 385 mg of the hydrogen maleate salt of compound A) Compound A hum ! 2. 77 (2mg base) Polyplasdne XL USP/NF 36. 00 Glyceryl monostearate USP/NF 9. 00 Poloxalkol 1. 80 Lactose 200 mesh 30. 53 HPMC 3cPs 4. 50

Polyethyleneglycol 4000 5.40 Water adsorbed 2.00 Total 92 mg Example 3 A 6 mg tablet formulation may be prepared by the manufacturing process described hereinafter. a) Preparation of the granulated material Preparation of the granulating solution 1. Approximately 40 kg of purified water are weighed out.

2. 3. 600 kg of methylhydroxypropylcellulose 3 maps are added to the purified water from step 1 while stirring until dissolution.

3. 1. 440 kg of poloxamer 188 are added to the solution from step 2 while stirring until dissolution (mixing tank under stirring).

Granulating step 4. 4. 787 kg of compound A hml and 28. 800 kg of crospovidone, 21. 853 kg of lactose monohydrate and 4. 320 kg of glyceryl monostearate are weighed out.

5. The ingredients from step 4 are mixed with the intensive mixer, e. g., Colette Grale 300 I or Fieldero (mixer speed setting : 1 ; chopper speed setting : 1) for approximately 2 minutes.

6. The mixture from step 5 is wetted with the granulating solution from step 3 while mixing with the intensive mixer, e.g., Colette Grale 300 1 or Fieldere (mixer speed setting : 1 ; chopper speed setting : 0 ; pumping rate approximately 4 kg/minute) for approximately 12 minutes.

7. Approximately 2 kg of purified water are weighed out.

8. The vessel from step 3 is rinsed with the purified water from step 7 and this is added to the mixture from step 6 while mixing.

9. The mass is granulated by mixing with the intensive mixer, e.g., Colette Grals 300 1 or Fieldere (mixer speed setting : 1 ; chopper speed setting : 1) for approximately 2. 5 minutes.

Drying step 10. The granulate from step 9 is dried in a fluidised air bed drier, e.g., Glatts or Aeromatic®) for approximately 65 minutes (Inlet air temperature approximately 70°C) to reach the desired loss on drying (LOD) for the tableting mixture, i. e., until LOD <4, 4%.

11. The granulate sized by sieving (0. 8 millimetres) with an oscillating sieve granulator (Frewitt or Erweka) 12. Steps 1 to 11 are repeated. b) Preparation of the tableting mixture 13. 8. 640 kg of polyethylene glycol 4000 and 5. 760 kg of glyceryl monostearate are sieved with an oscillating sieve granulator, e.g., Frewitte or Erwekas (0.8 millimetres) 14. The ingredients from step 13 are added to the total mass of granulated material and this is mixed with a free fall mixer, e. g., Soneco or Rohnrad, for approximately 20 minutes (10 rpm) in the desired final tableting mixture. c) Compression step 15. The tableting mixture from step 14 is pressed into tablets using compression pressures of 13,16 or 19 KN on a rotary tableting machine, e.g., Fette®, Korsh®, Keliane or Coarty (temperature <20°C, rH (relative humidity) < 40 %).

Example 4 : Composition of a 6 mg tablet (1 mg of base corresponds to 1.385 mu of hydroqen maieate of compound A) : Compound A hmt 8. 31 (6mg base) Polyplasdone XL USP/NF 50. 00 Glyceryl monostearate USP/NF 12. 50 Poloxalkol 2. 50 Lactose 200 mesh 37. 94 HPMC 3cPs 6. 25 Polyethyleneglycol 4000 7. 50 Water adsorbed 3. 00 Total 128 mg

Example 5 A 0. 5 mg tablet formulation may be prepared by the manufacturing process described hereinafter. a) Preparation of the granulated materia) Premixing step 1. 1. 994 kg of compound A hml and 31. 126 kg of lactose monohydrate are mixed with an intensive mixer (Colette GraIX 300 1 or Fielder®); mixer speed setting : 1 ; chopper speed setting : 1) for approximately 1. 5 minutes, or with a free fall mixer (Turbula®, Soneco or Rohnrad) 2. The premixture from step 1 is then sieved (oscillating granulator, e.g., Frewitte or Erweka#; mesh size : 0. 8 millimetres).

3. The premixture is divided into two portions of 16. 560 kg.

Preparation of the granulating solution 4. Approximately 43 kg of purified water are weighed out.

5. 3. 600 kg of methylhydroxypropylcellulose 3 maps are added to the purified water from step 4 and this is stirred until dissolution.

6. 1. 440 kg of poloxamer 188 are added to the solution from step 5 while stirring until dissolution.

Granu) ating step 7. 28. 800 kg of crospovidone, 10. 080 kg of lactose monohydrate and 4. 320 kg of glyceryl monostearate are weighed out.

8. One portion of the premixture from step 3 is added to the excipients from step 7 and this is mixed with the intensive mixer, e.g., Colette GralX 3001 or Fieldere (mixer speed setting : 1 ; chopper speed setting : 1) for approximately 2 minutes.

9. The mixture from step 8 is wetted with the granulating solution from step 6 while mixing with the intensive mixer, e.g., Colette Grals 300 1 or Fielder (mixer speed setting : 1 ; chopper speed setting : 0 ; pumping rate approximately : 4 kg/minute) for approximately 12 minutes.

10. Approximately 2 kg of purified water are weighed out.

11. The vessel from step 6 is rinsed with the purified water from step 10 and this is added to the mixture from step 9 while mixing.

12. The mass is granulated by mixing with the intensive mixer, Colette Gral# 300 1 or Fielder (mixer speed setting : 1 ; chopper speed setting : 1) for approximately 2. 5 minutes.

Drying step 13. The granulate from step 12 is dried in a fluidised air bed drier (e.g., Glatte or Aeromatic®) for approximately 60 minutes (inlet air temperature approximately 70°C) to reach the required loss on drying (LOD) for the tableting mixture, i. e. until LOD : 4, 5%.

14. The granulate sized by sieving (0. 8 millimetres) with an oscillating sieve granulator, e. g., Frewitte or Erweka.

15. Steps 4 to 14 are repeated with the other portion of step 3. b) Preparation of the tableting mixture 16. 8. 640 kg of polyethylene glycol 4000 and 5. 760 kg of glyceryl monostearate are sieved (oscillating granulator, e.g., Frewitte or Erweka#; mesh size : 0. 8 millimetres) 17. The ingredients from step 16 are added to the total mass of granulated material and this is mixed with a free fall mixer, e.g., Sonoco# or Röhrnad#, for approximately 20 minutes (10 rpm) to obtain the desired final tableting mixture. c) Compression step 18. The tableting mixture from step 17 is pressed into tablets on a rotary tableting machine, e.g., Fette®, Korsh®, Keliane or Coarty# (temperature < 20°C ; rH (relative humidity) < 40%) Example 6: Composition of a 0,5 mg tablet (1 mg of base corresponds to 1.385 mg of the hydrogen maleate salt of compound A) Compound A hml 0.6925 (0.5mg base) Polyplasdone XL USP/NF 20. 00 Glyceryl monostearate USP/NF 5. 00 Poloxalkol 1.00 Lactose 200 mesh 17. 8075 HPMC 3cPs 2. 50 Polyethyleneglycol 4000 3. 00 Water adsorbed 1. 00 Total 51 mg Exemple 7: Composition of a 12 mg tablet (1 mg of base corresponds to 1. 385 mg of the hydrogen maleate salt of compound A) The manufacturing process is similar to the process used for the 6mg tablets.

Compound A hml 16.62 (12mg base) Polyplasdone XL USP/NF 72. 00 Glyceryl monostearate USP/NF 18. 00 Poloxalkol 3.60 Lactose 200 mesh 49. 98 HPMC 3cPs 9. 0 Polyethyleneglycol 4000 10. 8 Water adsorbed 4. 00 Total 184 mg



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(WO/2000/010526) NEW ORAL FORMULATION FOR 5-HT4 AGONISTS OR ANTAGONISTS

Biblio. Data

Description

Claims

National Phase

Notices

Documents

Note: OCR Text

Claims : 1. A solid oral pharmaceutical composition comprising an effective amount of an acid sensitive active agent and a disintegrant which is present in an amount of at least 15% by weight based on the total weight of the composition.

2. A solid oral pharmaceutical composition comprising an effective amount of an active agent which is poorly soluble in aqueous media and a disintegrant which is present in an amount of at least 15% by weight based on the total weight of the composition.

3. A pharmaceutical composition according to claim 1 or 2 wherein the active agent has a solubility in aqueous media less than 1%.

4. A pharmaceutical composition according to any of claims 1 to 3 wherein the active agent is a serotonergic compound.

5. A pharmaceutical composition as claimed in any preceding claim wherein the active agent is a 5-HT4 receptor antagonist.

6. A pharmaceutical composition as claimed in any of claims 1 to 4 wherein the active agent is a 5-HT4 receptor agonist.

7. A pharmaceutical composition according to claim 6 wherein the 5-HT4 receptor agonist is Tegaserod, preferably its hydrogen maleate (hml) salt.

8. A pharmaceutical composition as claimed in any preceding claim wherein the disintegrant is crospovidone.

9. A pharmaceutical composition as claimed in any preceding claim comprising a lubricant.

10. A pharmaceutical composition according to claim 9 wherein the lubricant comprises a glyceryl mono fatty acid.

11. A pharmaceutical composition according to claim 9 wherein the lubricant comprises a mixture of glyceryl monostearate and polyethylene glycol.

12. A pharmaceutical composition as claimed in any preceding claim comprising a surfactant.

13. A pharmaceutical composition according to claim 12 wherein the surfactant comprises poloxamer.

14. Use of at least 15% by weight of a disintegrant in the manufacturing of a solid pharmaceutical composition for the administering of an acid sensitive active agent.

15. Use of at least 15% by weight of a disintegrant in the manufacturing of a solid pharmaceutical composition for the administering of an active agent being acid sensitive and/or having a poor water solubility.

16. Use according to claim 14 or 15 wherein the active agent is a 5-HT4 receptor agonist.
17. Use according to claim 16 wherein the 5-HT4 receptor agonist is Tegaserod, preferably its hydrogen maleate salt.
18. Use of a pharmaceutical composition according to any one of claims 1 to 13 for the the manufacture of a composition for the prevention and treatment of gastro-intestinal motility disorders in humans or animals.
19. A process for improving dissolution properties of a pharmaceutical composition as claimed in any of claims 1 to 13.
20. A method for preventing, modulating or treating visceral pain or discomfort, for modulating visceral sensitivity or perception, for improving sensory perception of rectal distension, or for treating anal continence dysfunctions in a subject in need thereof, which method comprises administering to said subject an effective amount of a 5-HT4 receptor agonist, partial agonist or antagonist or a pharmaceutically acceptable salt thereof.
21. A 5-HT4 receptor agonist, partial agonist or antagonist or a pharmaceutically acceptable salt thereof for use in the manufacture of a pharmaceutical composition for use in preventing, modulating or treating visceral pain or discomfort, modulating visceral sensitivity or perception, improving sensory perception of rectal distension, or treating anal continence dysfunctions.
22. A pharmaceutical composition for use in preventing, modulating or treating visceral pain or discomfort, modulating visceral sensitivity or perception, improving sensory perception of rectal distension, or treating anal continence dysfunctions, which composition comprises a 5-HT4 receptor agonist, partial agonist or antagonist or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable diluents or carriers therefor.
23. A method for preventing or treating gastro-intestinal motility disorders in horses or cattle in need thereof, which method comprises administering to the horses or cattle an effective amount of a 5-HT4 receptor agonist or partial agonist or a pharmaceutically acceptable salt thereof.
24. A 5-HT4 receptor agonist or partial agonist or a pharmaceutically acceptable salt thereof, for use as a veterinary pharmaceutical or for use in the manufacture of a veterinary pharmaceutical.
25. A pharmaceutical composition for veterinary use comprising a 5-HT4 receptor agonist or partial agonist or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier therefor.
26. A pharmaceutical composition comprising Tegaserod having dissolution characteristics in water or USP buffers pH 6.8 and 7.5 of : time (minutes) amount (percentage) 530-90 15 80 - 100 30 95 - 100 60 100